DETAILED ACTION

Status

Applicant's reply filed 10/06/2009 is acknowledged. Claims 18, 20, 21, 23, 31, 33, 36, 51 and 52 are pending.

All rejections made in the Office action mailed 03/12/2009 are withdrawn. With regard to claims 18, 20, 21, 23, and 51, Applicant's amendment to claim 18 to recite 2'-O-methyl-5-methyluridine-5'-triphosphate renders the claims non-obvious. With regard to claims 31, 33 and 36, Applicant's argument that there was insufficient teaching or suggestion to target the initiation region to search for initiation inhibitors is found persuasive.

New grounds of rejection are set forth below to address this issue. This Office action is NON-FINAL.

Drawings

The drawings were received on 08/12/2009. These drawings are accepted.

Oath/Declaration

The declaration submitted 09/20/2006 contains an error. Benefit was claimed for provisional application number 60/555,746. This provisional application has nothing to do with the instant application. The correct provisional application number is 60/555,765. Applicant is required to submit a supplemental application data sheet cancelling the claim to 60/555,746. The following guidelines are found in MPEP 601.05:

Supplemental application data sheets may be subsequently supplied prior to payment of the issue fee to either correct or update information in a previously submitted application data sheet, or an oath or declaration under 37 CFR 1.63 or 1.67. See 37 CFR 1.76(c)(1). A supplemental data sheet cannot be used to correct the following: (1)

inventorship changes (37 CFR 1.48); (2) correspondence changes (37 CFR 1.33(a)); and (3) citizenship changes (37 CFR 1.63 or 37 CFR 1.67). Supplemental application data sheets must be titled "Supplemental Application Data Sheet" and also contain all of the seven section headings listed in 37 CFR 1.76(b) with all appropriate data for each heading. Supplemental application data sheets identifying only the information that is being changed (added, deleted, or modified) in the supplemental ADS are not acceptable. A supplemental ADS containing only new or changed information is likely to confuse the record, create unnecessary work for the Office, and does not comply with 37 CFR 1.76. If no ADS was originally filed, but applicant wants to submit an ADS to correct, modify, or augment the original application data, the ADS, even though it is the first-filed ADS, must be titled "Supplemental Application Data Sheet."

A supplemental ADS that is being used to correct data shown in an oath or declaration, such as foreign priority or residence information for an inventor, would show the original incorrect information with strike-through or brackets, and the new information with underlining, as if an ADS had originally been used to submit the information. For example, if the original oath or declaration included a foreign priority claim, in order to delete the foreign priority claim, applicant should provide a supplemental ADS showing the foreign priority claim with strike-through or brackets to ensure that the patent will reflect such change.

Specification

Paragraph 0001 of the specification as filed contains an error. The filing date for provisional application 60/555,765 is indicated as January 6, 2003. The correct filing date for this provisional application is March 24, 2004. Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 23 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 23 recites "via a high specificity binding reaction". The term "high" in claim 23 is a relative term which renders the claim indefinite. The term "high" is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention. Applicant is advised to amend to "via a specific binding reaction".

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 31 and 36 are rejected under 35 U.S.C. 103(a) as being unpatentable over Hardy et al (Journal of Virology 77(3):2029-2037, February 2003, cited on the IDS of 09/20/2006) in view of Zhong et al (Antimicrobial Agents and Chemotherapy

47(8):2674-2681, August 2003, cited on the IDS of 09/20/2006) and Mueller et al (Journal of Biological Chemistry 261(25):11756-11764, September 1986).

With regard to claims 31 and 36, Hardy teaches a method for determining whether a test compound is an RNA synthesis inhibitor of a positive strand RNA virus (specifically hepatitis C virus) comprising:

contacting an isolated replicase complex for the positive strand RNA virus (Abstract: "A number of hepatitis C virus (HCV) proteins, including NS5B, the RNA-dependent RNA polymerase, were detected in membrane fractions from Huh7 cells containing autonomously replicating HCV RNA replicons. These membrane fractions were used in a cell-free system for the analysis of HCV RNA replication." Page 2031, column 2, last paragraph: "The P15 fractions enriched for HCV nonstructural proteins were assayed for replicase activity in the presence of a reaction mix...". Page 2030, paragraph bridging columns 1-2: "...we produced membrane fractions from cells harboring the subgenomic replicon. These fractions were shown to contain several HCV nonstructural proteins and RdRp activity. This system allows cell-free analysis of RNA replication by what is predicted to be a multicomponent HCV RNA replicase."),

an isolated viral replicon template RNA for the positive strand RNA virus (Page 2031, column 1, first paragraph of "Results": "The replicon RNA...was derived from the HCV genotype 1b...". Page 2031, column 2, last paragraph: "Since no additional RNA is added to the in vitro reaction mixture, the template corresponds to the endogenous replicon RNA."),

nucleotides (Page 2031, column 2, last paragraph: "…cold nucleoside triphosphates (NTPs)…". See also last paragraph, page 2030.),

and a labeled nucleotide analog (Page 2031, column 2, last paragraph: "…including [^{32}P]CTP…". See also last paragraph, page 2030.),

and the test compound (Page 2033, column 2, last paragraph: "Membrane fractions from cells containing the HCV replicon RNA were incubated for 5 min at 25°C in the presence of candidate inhibitory compounds…".)

under conditions sufficient for in vitro RNA synthesis, to form a newly synthesized RNA population comprising the labeled nucleotide analog (Page 2033, column 2, last paragraph: "Membrane fractions from cells containing the HCV replicon RNA were incubated for 5 min at 25°C in the presence of candidate inhibitory compounds…After this preincubation period, the remaining components of the standard replication reaction were added...and the reactions continued for 1 h at 34°C.");

detecting the newly synthesized RNA population comprising the labeled nucleotide analog (See figure 7. See also Materials and Methods, paragraph entitled "In vitro HCV RNA synthesis" bridging pages 2030-2031.);

quantitating the newly synthesized RNA population comprising the labeled nucleotide analog to provide a test RNA amount (See figure 7 caption: "...quantitated by using a phosphorimager...".);

and comparing the test RNA amount with a control RNA amount of a control newly synthesized RNA population comprising the labeled nucleotide analog produced in the absence of the test compound (See figure 7; the graph clearly indicates a 0 μM

inhibitor data point, which represents a reaction performed in the absence of the inhibitor, i.e. test compound.)

wherein a decrease in the test RNA amount compared to the control RNA amount indicates that the test compound inhibits RNA synthesis of the positive strand RNA virus (See figure 7, which indicates that the amount of test RNA, as measured by the incorporation of the labeled nucleotide, decreases with increasing concentration of inhibitor.).

Hardy does not teach *hybridizing a probe and the newly synthesized RNA population comprising the labeled nucleotide analog, under stringent conditions, wherein the probe is complementary to at least a portion of an initiation region of the newly synthesized RNA population; digesting unhybridized, single-stranded RNA with a single-strand specific ribonuclease to form a protected RNA population comprising the labeled nucleotide analog; detecting the protected RNA population comprising the labeled nucleotide analog; quantitating the protected RNA population comprising the labeled nucleotide analog; and comparing the test RNA amount with a control RNA amount of protected RNA* to determine whether *the test compound inhibits RNA synthesis initiation of the positive strand virus.*

In other words, the difference between the claimed invention and Hardy is that Hardy does not carry out and RNase protection assay using a probe to the RNA synthesis (transcription) initiation region to assess RNA synthesis *initiation* (Hardy just quantifies the final transcript).

Zhong taught dinucleotide analogs as inhibitors of hepatitis C virus, specifically as inhibitors of RNA synthesis initiation:

Abstract: "Because the initiation process is a rate-limiting step in viral RNA replication, inhibitors that interfere with the initiation process will have advantages in suppressing virus replication."

Page 2674, last paragraph: "The use of dinucleotide analogues as inhibitor molecules to target the initiation step of viral RNA synthesis represents a novel approach to antiviral interference."

It was known in the prior art to hybridize a probe to the transcription initiation region of a transcript followed by RNase digestion to assess transcription initiation. As in the claimed methods, Mueller synthesized newly transcribed RNA comprising a labeled nucleotide analog and hybridized the newly synthesized RNA with a probe (unlabeled), followed by digestion of the unprotected RNA.

In particular, Mueller taught an assay comprising *hybridizing a probe and the newly synthesized RNA population comprising the labeled nucleotide analog* (See page 11758, column 1, 2nd and 3rd paragraphs for the synthesis of newly synthesized RNA population comprising a labeled nucleotide analog (i.e. ^{32}P-labeled); see page 11758, column 1, paragraph entitled "Hybridization and Digestion of the RNA/DNA Hybrid"; see paragraph bridging pages 11758-9; see page 11759, paragraph bridging columns 1-2: "The clones, serving as probes of the 21 S rDNA, 14 S rDNA, Oli-1, $tRNA^{Cys}$, and the $tRNA_f^{Met}$ genes, overlap the transcriptional promoter in each case. This allowed an

assessment of the fidelity of transcriptional initiation as well as of the rates of transcription."),

under stringent conditions (see page 11758, column 1, paragraph entitled "Hybridization and Digestion of the RNA/DNA Hybrid"; the term "stringent conditions" does not distinguish over the conditions taught by Mueller),

wherein the probe is complementary to at least a portion of an initiation region of the newly synthesized RNA population (see page 11759, paragraph bridging columns 1-2: "The clones, serving as probes of the 21 S rDNA, 14 S rDNA, Oli-1, $tRNA^{Cys}$, and the $tRNA_f^{Met}$ genes, overlap the transcriptional promoter in each case. This allowed an assessment of the fidelity of transcriptional initiation as well as of the rates of transcription.");

digesting unhybridized, single-stranded RNA with a single-strand specific ribonuclease to form a protected RNA population comprising the labeled nucleotide analog (see page 11758, column 1, paragraph entitled "Hybridization and Digestion of the RNA/DNA Hybrid"; see paragraph bridging pages 11758-9);

detecting the protected RNA population comprising the labeled nucleotide analog (see page 11758, column 2, paragraph entitled "Gel Electrophoresis of the Samples");

quantitating the protected RNA population comprising the labeled nucleotide analog (see page 11758, column 2, paragraph entitled "Quantitation of the Autoradiogram").

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to modify the method of Hardy to specifically assess

transcription initiation because Zhong clearly stated that inhibitors of transcription initiation provided advantages. Therefore, one would have been motivated to use the known technique described by Mueller for assessing transcription initiation.

Response to Arguments

Applicant's arguments with respect to claims 31 and 36 have been considered but are moot in view of the new ground(s) of rejection. In particular, a clear rationale for assessing transcription initiation has been provided. With regard to Applicant's arguments that Mueller is irrelevant, since he was studying yeast and not HCV, this argument is not persuasive. One of skill in the art understood that general molecular biology techniques such as taught by Mueller were applicable across diverse fields of study.

Conclusion

Claims 18, 20, 21, 51 and 52 are allowed. Claim 23 would be allowable in accordance with the examiner's suggestion above.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to SAMUEL C. WOOLWINE whose telephone number is (571)272-1144. The examiner can normally be reached on Mon-Fri 9:00am-5:00pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion can be reached on (571) 272-0782. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Samuel Woolwine/
Examiner, Art Unit 1637